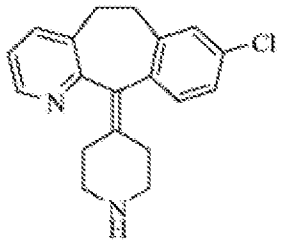
REMARKS

An aspect of the present invention is to deliver alternative pharmaceuticals to the U.S. market so as to foster competition. An average consumer benefits from the delivery of alternative pharmaceuticals to the U.S. market because the presence of alternative pharmaceuticals affords the average consumer with greater selection, which, in turn, reduces the overall costs for pharmaceuticals. With this aim in mind, Applicants have sought to develop alternative forms of desloratadine, known as 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, and represented by the following structure:



Desloratadine is currently marketed as CLARINEX® in the United States. CLARINEX® is prescribed as an antihistamine for prevention or treatment of allergenic reactions, which may result in symptoms such as sneezing, itchy eyes and hives.

Desloratadine in crystalline distinct forms currently enjoys patent protection by way of U.S. Patent No. 6,506,767 ("'767 patent"). The '767 patent discloses two polymorphic forms of desloratadine, labeled form 1 and form 2, which is synonymous to "Form I" and "Form II," respectively, as used in Applicants' disclosure. Indeed, the discovery of the '767 patent is that desloratadine "can exist in the form of two *distinct* crystalline polymorphs, each having distinctly different physical properties (see the '767 patent at col. 1, lines 45-47, with emphasis added.).

The Examiner's attention is directed to the text of the '767 patent at column 1, lines 48-50, for a discussion of a first distinct crystalline form, which discloses that "this invention provides crystalline polymorph form 1 [desloratadine] essentially free of polymorph form 2." The '767 patent at column 3, lines 53-58 specifies that "the phrase 'polymorph form 1 essentially free of polymorph form 2' as used herein means that [desloratadine] polymorph form 1 prepared

in accordance with this invention contains less than about 1% of form 2 as measured by infrared spectral analysis on a FTIR spectrometer." In other words, a first aspect of the '767 patent is to have a crystalline sample of [desloratadine] consisting of an amount of form 1 that exceeds about 99%, with the remainder being form 2. This aspect is bolstered by the disclosure of the '767 patent at column 3, lines 58-60, which reads "[t]he polymorph form 1 prepared in accordance with Examples 1 and 2 had no detectable amount of form 2 by FTIR spectrophotometry."

The Examiner's attention is also directed to the text of the '767 patent at column 2, lines 50-52, for a discussion of a second distinct crystalline form, which discloses that the "invention also provides crystalline polymorph form 2 [desloratadine] substantially free of poymorph [sic] form 1." The '767 patent at column 3, lines 60-67 specifies that "the phrase 'polymorph form 2 substantially free of polymorph form 1' as used herein means that the [desloratadine] polymorph form 2 prepared in accordance with this invention contains less than about 15%, preferably less than about 10%, and more preferably less than about 5-8% of form 1 as measured by infrared spectral analysis on a FTIR spectrometer." In other words, a second aspect of the '767 patent is to have a crystalline sample of [desloratadine] consisting of an amount of form 2 that exceeds about 85%, with the remainder being form 1.

In summary, an aim of the '767 patent is to have polymorph form 1 that is essentially free of polymorph form 2, which means that the amount of polymorph form 1 exceeds about 99%, with the remainder being form 2. Another aim of the '767 patent is to have polymorph form 2 that is substantially free of polymorph form 1, which means that the amount of polymorph form 2 exceeds about 85%, with the remainder being form 1. These aspects are summarized in the following Table.

Composition	form 1	form 2
form 1 essentially free of form 2	greater than about 99% (range: >99%-100%)	less than about 1% (range: <1%-0%)
form 2 substantially free of form 1	less than about 15% (range: <15%-0%)	greater than about 85% (range: >85%-100%)

In short, one can infer that the intent of the '767 patent is to obtain crystalline desloratadine in its two separate forms that are as pure as possible. This can be understood by inspecting the disclosure of the '767 patent at col. 1, lines 34-41, which reads as follows with emphasis added:

> To prepare pharmaceutical compositions containing [desloratadine] for administration to mammals in accordance with exacting health registration requirements of the U.S. and international health registration authorities, e.g. the FDA's Good Manufacturing Practices("GMP")requirements, there is **a need to produce [desloratadine] in as pure a form as possible**, especially a form having constant physical properties.

The '767 patent further discloses at column 4, lines 5-11 that:

> We have discovered that [desloratadine] exists as a mixture of polymorphs. Such a mixture could lead to production of a [desloratadine] product which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.

Based on the forgoing, one can infer that the intent of the '767 patent is to provide two distinct crystalline forms of desloratadine in which each form is produced "in as pure as form as possible, especially a form having constant physical properties" (see the '767 patent at col. 1, lines 40-41). One can also infer that it is unacceptable to have crystalline desloratadine that is not in as pure a form as possible, because the crystalline material would not have constant physical properties, which is "unacceptable in view of stringent GMP requirements" (see the '767 patent at col. 4, lines 9-11).

Accordingly, the rejection of claims 1-13, 15-26, and 28-59 under 35 U.S.C. § 103(a) over the disclosure of the '767 patent is respectfully traversed.

The present invention is unobvious over the '767 patent for at least the following two reasons. First, the '767 patent does not disclose or suggest the presently claimed ratios, as acknowledged by the Office. Second, the '767 patent discloses that it is undesirable to administer desloratadine to a mammal unless it is in a form that is as pure as that disclosed in the '767 patent.

The Office has acknowledged that the "Schumacher '767 patent does not explicitly teach the instantly claimed weight percent ranges and ratios of polymorph Form I to Form II of desloratadine present within said stable mixture" (see August 16, 2006 Office Action at page 10,

lines 6-8). So there is no issue as to whether the presently claimed weight ratios of desloratadine Form I-to-Form II overlap between the weight ratios of desloratadine that is disclosed in the '767 patent.

Instead, the Office has taken the position that Applicants' claimed invention is merely an optimization of that which is disclosed in the '767 patent (see pages 10-11 of August 16, 2006 Office Action). In other words, the Office has taken the position that it is acceptable to have crystalline desloratadine that is not as pure as that which is prescribed by the '767 patent. Applicants believe that this position is without merit because it diverges from the suggestion offered by the '767 at column 1, lines 34-41 and column 4, lines 5-11 that it is unacceptable to have desloratadine crystalline forms that are not as pure as possible. In other words, Applicants believe that the '767 patent mandates that it is unacceptable to have crystalline polymorph Form I of desloratadine unless it is essentially free of polymorph form 2. Moreover, Applicants believe that the '767 patent also mandates that it is unacceptable to have crystalline polymorph Form II of desloratadine unless substantially free of polymorph Form I.

Applicants ask that the Office acknowledge that the '767 patent actually teaches away from the presently claimed invention upon consideration of the following passage from the *Gurley Court*, with emphasis added:

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or **would be led in a direction divergent from the path that was taken by the applicant**.

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994), which has been followed and cited with approval in numerous other Federal Circuit decisions.

Applicants also ask that the Examiner consider Applicants' stability results disclosed on pages 17-18 of the Specification, and reproduced below for convenience.

	Example 1 Stability Tests, page 17				Example 2 Stability Tests, page 17			
	25°C, 60%RH		40°C, 75%RH		25°C, 60%RH		40°C, 75%RH	
time (weeks)	Form I	Form II	Form I	Form II	Form I	Form II	Form I	Form II
0	57	43	57	43	62	38	62	38
1	59	41	46	54	65	35	63	37
2	53	47	43	57	61	39	64	36
4	55	45	50	50	66	34	65	35
8	63	37	39	61	67	33	65	35
12	52	48	—	—	66	34	—	—
Average (%)	57	44	47	53	65	36	64	36
Stddev (%)	4	4	7	7	2	2	1	1

	Example 3 Stability Tests, page 18				Example 4 Stability Tests, page 18			
	25°C, 60%RH		40°C, 75%RH		25°C, 60%RH		40°C, 75%RH	
time (weeks)	Form I	Form II	Form I	Form II	Form I	Form II	Form I	Form II
0	74	26	74	26	76	24	76	24
1	79	21	77	23	87	13	76	24
2	74	26	81	19	80	20	82	18
4	79	21	78	22	82	18	88	12
8	75	25	78	22	86	14	85	15
12	74	26	75	25	81	19	82	18
24	77	23	75	25	84	16	82	18
Average (%)	76	24	77	23	82	18	82	18
Stddev (%)	2	2	2	2	4	4	4	4

The data represents the percentage of each crystalline form as a function of time, as measured by X-ray powder diffraction (see present Specification at page 15, lines 1-5). The compositions were obtained by recrystallization of desloratadine using certain solvent mixtures. For example, the crystalline material reported in Example 1, see page 17, lines 9-15, was obtained by recrystallizing 3 g of desloratadine from dimethyl carbonate-diethyl carbonate (1:1, 35 mL at 110°C. The Table includes the average percentage of each crystalline form over the reported period of time. As can be seen from the Table, stable mixtures were obtained even though the crystalline forms are not as "pure" as that prescribed by the '767 patent. The Office is reminded that the '767 patent discloses that it is unacceptable to have "variable percent amounts

of polymorphs" since these variable compositions would have "variable physical properties," which is "a situation unacceptable in view of stringent GMP requirements" (see the '767 patent at col. 4, lines 5-11). Yet, Applicants disclosure at page 14, lines 9-15, discloses that:

> The physical properties of the two separate polymorphs (Form I and Form II) were compared to the physical properties of some mixtures (25:75, 50:50, 75:25, 84:16 Form I:Form II). It was discovered that polymorphic mixtures with different polymorphic compositions have practically invariable physical properties as compared to the separate polymorphs (Form I and Form II). Hence, even if there is polymorphic transformation, the thermal characteristics of the polymorphic mixture may retain substantially the same, which is ideal for formulation.

In other words, Applicants have shown that mixtures of desloratadine are stable. This information is unexpected when one considers the mandate of the '767 patent, i.e., that variable compositions have variable physical properties.

In view of the foregoing, Applicants believe that the present invention is unobvious over the disclosure of the '767 patent because: the '767 patent does not disclose or suggest the claimed elements, the '767 patent teaches away from the claimed subject matter, and the results of the present application are unexpected when compared to the disclosure of the '767 patent. Applicants kindly request that the Examiner acknowledge the same and withdraw this rejection.

The provisional rejection of claims 1-13, 15-26, and 28-59 under the judicially created doctrine of obviousness-type double patenting over claims 21-24 of pending application 11/283,276 ("the '276 application") is respectfully traversed.

Claims 21-24 of the '276 application are reproduced below:

> 21. A mixture of crystalline Form I and Form II of desloratadine, containing about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof.
>
> 22. The mixture of claim 21, comprising about 35-82% desloratadine Form I and about 18-65% desloratadine Form II.

23. The mixture of claim 22, comprising about 55-82% desloratadine Form I and about 18-45% desloratadine Form II.

24. A pharmaceutical formulation comprising the mixture of claim 21.

Although it may be true that claim 21 is directed to crystalline desloratadine comprising a mixture of Form I and Form II, claim 21 also recites that the mixture comprises "about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof." This should be contrasted with each of Claims 1, 15, 28, 29, 37, and 49, in which there is no requirement to have a crystalline mixture that comprises "about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof."

Applicants kindly request that the Examiner withdraw this rejection.

Applicants concurrently filed with the present response an **Information Disclosure Statement** citing U.S. Patent 6,335,347 and copending application 10/800,290 ("the '290 application"), filed March 12, 2004 and published as US 2004/0242619 on December 2, 2004. Acknowledgement of these references is kindly requested.

Applicants concurrently filed with the present response a Request for a Three-Month Extension of Time under 37 CFR 1.136(a) with an authorization to charge the requisite fee under 37 CFR 1.17(a)(3) to Applicants' representative Deposit Account 13-2725. If for any reason the Request is separated from the present response, then Applicants authorize the Office to charge the above-noted Deposit Account to pay any necessary fees so as to maintain the pendency of the present application.

Applicants believe that the present application is now in a condition for allowance. In the event that the Examiner acknowledges the same, then Applicants kindly request rejoinder of withdrawn claims 14, 27, and 60.

In view of the remarks contained herein, Applicants respectfully request a Notice of Allowance. If the Examiner believes that a discussion would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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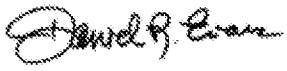

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Date: February 21, 2007